IN THE UNITED STATES PATENT OFFICE

I, Stephen DRANE BSc PhD BDÜ,
translator to RWS Translations Ltd., of Europa House, Marsham Way, Gerrards Cross, Buckinghamshire, England declare;

1. That I am a citizen of the United Kingdom of Great Britain and Northern Ireland.

2. That I am well acquainted with the German and English languages.

3. That the attached is, to the best of my knowledge and belief, a true translation into the English language of the accompanying copy of the specification filed with the application for a patent in Germany on 14 October 1994 under the number P 44 36 851.8 and the official certificate attached hereto.

4. That I believe that all statements made herein of my own knowledge are true and that all statements made on information and belief are true; and further that these statements are made with the knowledge that wilful false statements and the like so made are punishable by fine or imprisonment, or both, under Section 1001 of Title 18 of the United States Code and that such wilful false statements may jeopardise the validity of the patent application in the United States of America or any patent issuing thereon.

For and on behalf of RWS Translations Ltd.

The 26th day of February 1998

FEDERAL REPUBLIC OF GERMANY

CERTIFICATE

BASF Aktiengesellschaft

of

67056 Ludwigshafen

have filed a Patent Application under the title:

"Novel carboxylic acid derivatives, their preparation and use"

on 14 October 1994 at the German Patent Office.

The attached document is a correct and accurate reproduction of the original submission for this Patent Application.

The German Patent Office has for the time being given the Application the symbols C 07 D 239/60, C 07 D 251/30, C 07 D 239/78, C 07 D 471/04, C 07 D 491/04, C 07 D 495/04, C 07 D 403/12, C 07 D 417/12, C 07 D 413/12, C 07 D 401/12, A 61 K 31/505 and A 61 K 31/53 of the International Patent Classification.

Munich, 4 September 1995

President of the German Patent Office

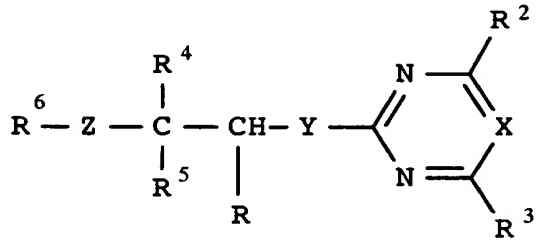
pp

Hoiß

File No: P 44 36 851.8

We claim:

A carboxylic acid derivative of the formula I



I

where R is formyl, a COOH group or a radical which can be hydrolyzed to COOH, and the other substituents have the following meanings:

R^2 halogen, C_1-C_4-alkyl, C_1-C_4-haloalkyl, C_1-C_4-alkoxy, C_1-C_4-haloalkoxy or C_1-C_4-alkylthio;

X nitrogen or CR^{14} where R^{14} is hydrogen or C_{1-5}-alkyl, or CR^{14} forms together with CR^3 a 5- or 6-membered alkylene or alkenylene ring which can be substituted by one or two C_{1-4}-alkyl groups and in which in each case a methylene group can be replaced by oxygen, sulfur, -NH or -NC_{1-4}-alkyl;

R^3 halogen, C_1-C_4-alkyl, C_1-C_4-haloalkyl, C_1-C_4-alkoxy, C_1-C_4-haloalkoxy, -NH-O-C_{1-4}-alkyl, C_1-C_4-alkylthio or CR^3 is linked to CR^{14} as indicated above to give a 5- or 6-membered ring;

R^4 and R^5 (which can be identical or different):

phenyl or naphthyl, which can be substituted by one or more of the following radicals: halogen, nitro, cyano, hydroxyl, C_1-C_4-alkyl, C_1-C_4-haloalkyl, C_1-C_4-alkoxy, C_1-C_4-haloalkoxy, phenoxy, C_1-C_4-alkylthio, amino, C_1-C_4-alkylamino or C_1-C_4-dialkylamino; or

phenyl or naphthyl, which are connected together in the ortho positions via a direct linkage, a methylene, ethylene or ethenylene group, an oxygen or sulfur atom or an SO_2, NH or N-alkyl group;

R^6 hydrogen, C_1-C_8-alkyl, C_3-C_6-alkenyl, C_3-C_6-alkynyl or C_3-C_8-cycloalkyl, where each of these radicals can be substituted one or more times by: halogen, nitro, cyano,

C_1-C_4-alkoxy, C_3-C_6-alkenyloxy, C_3-C_6-alkynyloxy, C_1-C_4-alkylthio, C_1-C_4-haloalkoxy, C_1-C_4-alkylcarbonyl, C_1-C_4-alkoxycarbonyl, C_{3-8}-alkylcarbonylalkyl, C_1-C_4-alkylamino, di-C_1-C_4-alkylamino, phenyl, or phenyl or phenoxy which is substituted one or more times, eg. one to three times, by halogen, nitro, cyano, C_1-C_4-alkyl, C_1-C_4-haloalkyl, C_1-C_4-alkoxy, C_1-C_4-haloalkoxy or C_1-C_4-alkylthio;

phenyl or naphthyl, each of which can be substituted by one or more of the following radicals: halogen, nitro, cyano, hydroxyl, amino, C_1-C_4-alkyl, C_1-C_4-haloalkyl, C_1-C_4-alkoxy, C_1-C_4-haloalkoxy, phenoxy, C_1-C_4-alkylthio, C_1-C_4-alkylamino, C_1-C_4-dialkylamino, dioxomethylene [sic] or dioxoethylene [sic];

a five- or six-membered heteroaromatic moiety containing one to three nitrogen atoms and/or one sulfur or oxygen atom, which can carry one to four halogen atoms and/or one or two of the following radicals: C_1-C_4-alkyl, C_1-C_4-haloalkyl, C_1-C_4-alkoxy, C_1-C_4-haloalkoxy, C_1-C_4-alkylthio, phenyl, phenoxy or phenylcarbonyl, it being possible for the phenyl radicals in turn to carry one to five halogen atoms and/or one to three of the following radicals: C_1-C_4-alkyl, C_1-C_4-haloalkyl, C_1-C_4-alkoxy, C_1-C_4-haloalkoxy and/or C_1-C_4-alkylthio;

Y sulfur or oxygen or a single bond;

Z sulfur or oxygen or a single bond.

Novel carboxylic acid derivatives, their preparation and use

The present invention relates to novel carboxylic acid derivatives, their preparation and use.

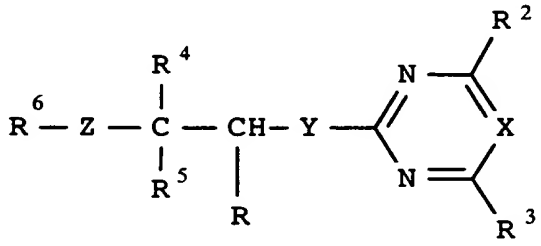
Endothelin is a peptide which is composed of 21 amino acids and is synthesized and released by the vascular endothelium. Endothelin exists in three isoforms, ET-1, ET-2 and ET-3. In the following text, "endothelin" or "ET" signifies one or all isoforms of endothelin. Endothelin is a potent vasoconstrictor and has a potent effect on vessel tone. It is known that this vasoconstriction is caused by binding of endothelin to its receptor (Nature, 332, (1988) 411-415; FEBS Letters, 231, (1988) 440-444 and Biochem. Biophys. Res. Commun., 154, (1988) 868-875).

Increased or abnormal release of endothelin causes persistent vasoconstriction in the peripheral, renal and cerebral blood vessels, which may lead to illnesses. It has been reported in the literature that elevated plasma levels of endothelin were found in patients with hypertension, acute myocardial infarct, pulmonary hypertension, Raynaud's syndrome, atherosclerosis and in the airways of asthmatics (Japan J. Hypertension, 12, (1989) 79, J. Vascular Med. Biology 2, (1990) 207, J. Am. Med. Association 264, (1990) 2868).

Accordingly, substances which specifically inhibit the binding of endothelin to the receptor ought also to antagonize the various abovementioned physiological effects of endothelin and therefore be valuable drugs.

We have found that certain carboxylic acid derivatives are good inhibitors of endothelin receptors.

The invention relates to carboxylic acid derivatives of the formula I



I

where R is formyl, a COOH group or a radical which can be hydrolyzed to COOH, and the other substituents have the following meanings:

R^2 halogen, C_1-C_4-alkyl, C_1-C_4-haloalkyl, C_1-C_4-alkoxy, C_1-C_4-haloalkoxy or C_1-C_4-alkylthio;

X nitrogen or CR^{14} where R^{14} is hydrogen or C_{1-5}-alkyl, or CR^{14} forms together with CR^3 a 5- or 6-membered alkylene or alkenylene ring which can be substituted by one or two C_{1-4}-alkyl groups and in which in each case a methylene group can be replaced by oxygen, sulfur, -NH or -NC_{1-4}-alkyl;

R^3 halogen, C_1-C_4-alkyl, C_1-C_4-haloalkyl, C_1-C_4-alkoxy, C_1-C_4-haloalkoxy, -NH-O-C_{1-4}-alkyl, C_1-C_4-alkylthio or CR^3 is linked to CR^{14} as indicated above to give a 5- or 6-membered ring;

R^4 and R^5 (which can be identical or different):

phenyl or naphthyl, which can be substituted by one or more of the following radicals: halogen, nitro, cyano, hydroxyl, C_1-C_4-alkyl, C_1-C_4-haloalkyl, C_1-C_4-alkoxy, C_1-C_4-haloalkoxy, phenoxy, C_1-C_4-alkylthio, amino, C_1-C_4-alkylamino or C_1-C_4-dialkylamino; or

phenyl or naphthyl, which are connected together in the ortho positions via a direct linkage, a methylene, ethylene or ethenylene group, an oxygen or sulfur atom or an SO_2-, NH- or N-alkyl group;

R^6 hydrogen, C_1-C_8-alkyl, C_3-C_6-alkenyl, C_3-C_6-alkynyl or C_3-C_8-cycloalkyl, where each of these radicals can be substituted one or more times by: halogen, nitro, cyano, C_1-C_4-alkoxy, C_3-C_6-alkenyloxy, C_3-C_6-alkynyloxy, C_1-C_4-alkylthio, C_1-C_4-haloalkoxy, C_1-C_4-alkylcarbonyl, C_1-C_4-alkoxycarbonyl, C_{3-8}-alkylcarbonylalkyl, C_1-C_4-alkylamino, di-C_1-C_4-alkylamino, phenyl, or phenyl or phenoxy which is substituted one or more times, eg. one to three times, by halogen, mitro, cyano, C_1-C_4-alkyl, C_1-C_4-haloalkyl, C_1-C_4-alkoxy, C_1-C_4-haloalkoxy or C_1-C_4-alkylthio;

phenyl or naphthyl, each of which can be substituted by one or more of the following radicals: halogen, nitro, cyano, hydroxyl, amino, C_1-C_4-alkyl, C_1-C_4-haloalkyl, C_1-C_4-alkoxy, C_1-C_4-haloalkoxy, phenoxy, C_1-C_4-alkylthio, C_1-C_4-alkylamino,

C_1-C_4-dialkylamino, dioxomethylene [sic] or dioxoethylene [sic];

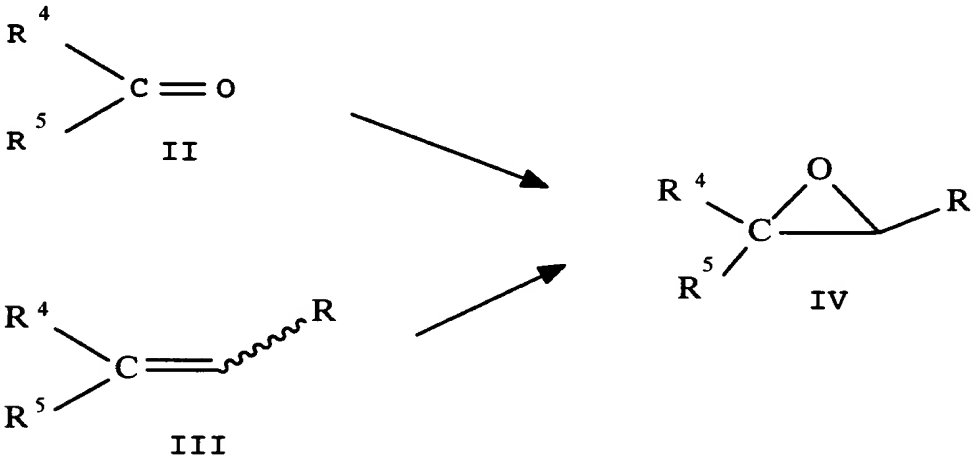
a five- or six-membered heteroaromatic moiety containing one to three nitrogen atoms and/or one sulfur or oxygen atom, which can carry one to four halogen atoms and/or one or two of the following radicals: C_1-C_4-alkyl, C_1-C_4-haloalkyl, C_1-C_4-alkoxy, C_1-C_4-haloalkoxy, C_1-C_4-alkylthio, phenyl, phenoxy or phenylcarbonyl, it being possible for the phenyl radicals in turn to carry one to five halogen atoms and/or one to three of the following radicals: C_1-C_4-alkyl, C_1-C_4-haloalkyl, C_1-C_4-alkoxy, C_1-C_4-haloalkoxy and/or C_1-C_4-alkylthio;

Y sulfur or oxygen or a single bond;

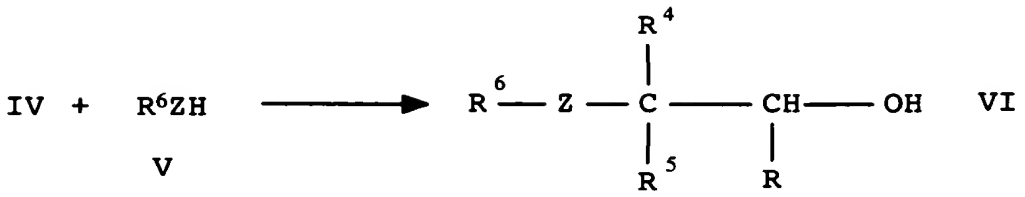
Z sulfur or oxygen or a single bond.

The invention furthermore relates to the use of the abovementioned carboxylic acid derivatives for producing drugs, in particular for producing endothelin receptor inhibitors.

The preparation of the compounds according to the invention where Z is sulfur or oxygen starts from the epoxides IV, which are obtained in a conventional manner, eg. as described in J. March, Advanced Organic Chemistry, 2nd ed., 1983, page 862 and page 750, from the ketones II or the olefins III:



Carboxylic acid derivatives of the general formula VI can be prepared by reacting the epoxides of the general formula IV (eg. with R = $ROOR^{10}$ [sic]) with alcohols or thiols of the general formula V where R^6 and Z have the meanings stated in claim 1.



To do this, compounds of the general formula IV are heated with a compounds [sic] of the formula V, in the molar ratio of about 1:1 to 1:7, preferably 1 to 3 mole equivalents, to 50-200°C, preferably 80-150°C.

The reaction can also take place in the presence of a diluent. All solvents which are inert toward the reagents used can be used for this purpose.

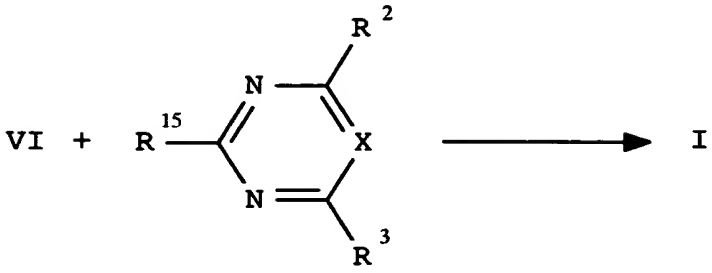
Examples of such solvents or diluents are water, aliphatic, alicyclic and aromatic hydrocarbons, which may in each case be chlorinated, such as hexane, cyclohexane, petroleum ether, naphtha, benzene, toluene, xylene, methylene chloride, chloroform, carbon tetrachloride, ethyl chloride and trichloroethylene, ethers such as diisopropyl ether, dibutyl ether, propylene oxide, dioxane and tetrahydrofuran, ketones such as acetone, methyl ethyl ketone, methyl isopropyl ketone and methyl isobutyl ketone, nitriles such as acetonitrile and propionitrile, alcohols, such as methanol, ethanol, isopropanol, butanol and ethylene glycol, esters such as ethyl acetate and amyl acetate, amides such as dimethylformamide and dimethylacetamide, sulfoxides and sulfones, such as dimethyl sulfoxide and sulfolane, bases such as pyridine, cyclic ureas such as 1,3-dimethylimidazolidin-2-one and 1,3-dimethyl-3,4,5,6-tetra-hydro-2(1H)-pyrimidinone.

The reaction is preferably carried out at a temperature in the range from 0°C to the boiling point of the solvent or mixture of solvents.

The presence of a catalyst may be advantageous. Suitable catalysts are strong organic and inorganic acids, and Lewis acids. Examples thereof are, inter alia, sulfuric acid, hydrochloric acid, trifluoroacetic acid, boron trifluoride etherate and titanium(IV) alcoholates.

The compounds according to the invention where Y is oxygen, and the remaining substituents have the meanings stated under the general formula I, can be prepared, for example, by reacting the carboxylic acid derivatives of the general formula VI where the

substituents have the stated meanings with compounds of the general formula VII



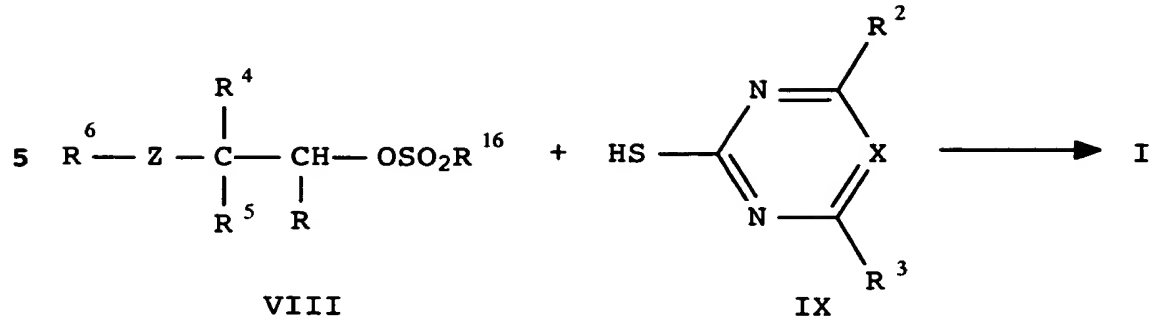
VII

where R^{15} is halogen or $R^{16}-SO_2-$, where R^{16} can be C_1-C_4-alkyl, C_1-C_4-haloalkyl or phenyl. The reaction preferably takes place in one of the abovementioned inert diluents with the addition of a suitable base, ie. of a base which deprotonates the intermediate VI, in a temperature range from room temperature to the boiling point of the solvent.

Compounds of the formula VII are known, some of them can be bought, or they can be prepared in a generally known manner.

It is possible to use as base an alkali metal or alkaline earth metal hydride such as sodium hydride, potassium hydride or calcium hydride, a carbonate such as an alkali metal carbonate, eg. sodium or potassium carbonate, an alkali metal or alkaline earth metal hydroxide such as sodium or potassium hydroxide, an organometallic compound such as butyllithium, or an alkali metal amide such as lithium diisopropylamide.

The compounds according to the invention where Y is sulfur, and the remaining substituents have the meanings stated under the general formula I, can be prepared, for example, by reacting carboxylic acid derivatives of the general formula VIII, which can be obtained in a known manner from compounds of the general formula VI and in which the substituents have the abovementioned meanings, with compounds of the general formula IX, where R^2, R^3 and X have the meanings stated under general formula I.

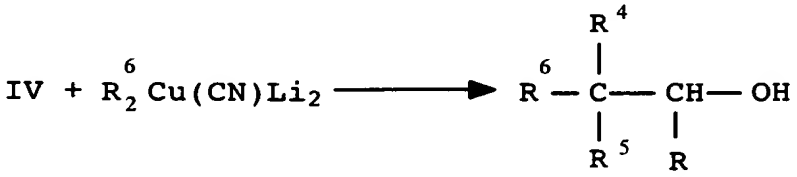


VIII IX I

The reaction preferably takes place in one of the abovementioned inert diluents with the addition of a suitable base, ie. a base which deprotonates the intermediate IX, in a temperature range from room temperature to the boiling point of the solvent.

It is possible to use as base, besides those mentioned above, organic bases such as triethylamine, pyridine, imidazole or diazabicycloundecane [sic].

Carboxylic acid derivatives of the formula VI (z = direct linkage) can be prepared by reacting epoxides of the formula IV with cuprates of the formula XI:



XI VIa

The cuprates can be prepared as described in Tetrahedron Letters 23, (1982) 3755.

Compounds of the formula I can also be prepared by starting from the corresponding carboxylic acids, ie. compounds of the formula I where R' [sic] is hydroxyl, and initially converting these in a conventional manner into an activated form, such as a halide, an anhydride or imidazolide, and then reacting the latter with an appropriate hydroxy compound HOR^{10}. This reaction can be carried out in the usual solvents and often requires addition of a base, in which case those mentioned above are suitable. These two steps can also be simplified, for example, by allowing the carboxylic acid to act on the hydroxy compound in the presence of a dehydrating agent such as a carbodiimide.

In addition, it is also possible for compounds of the formula I to be prepared by starting from the salts of the corresponding carboxylic acids, ie. from compounds of the formula I where R is COR^1 and R^1 is OM, where M can be an alkali metal cation or the equivalent of an alkaline earth metal cation. These salts can be reacted with many compounds of the formula R^1-A where A is a conventional nucleofugic leaving group, for example halogen such as chlorine, bromine, iodine or aryl- or alkylsulfonyl which is unsubstituted or substituted by halogen, alkyl or haloalkyl, such as toluenesulfonyl and methylsulfonyl, or another equivalent leaving group. Compounds of the formula R^1-A with a reactive substituent A are known or can be easily obtained with general expert knowledge. This reaction can be carried out in conventional solvents and advantageously takes place with the addition of a base, in which case those mentioned above are suitable.

The radical R in formula I may vary widely. For example, R is a group

where R^1 has the following meanings:

a) hydrogen;

b) succinylimidoxy [sic];

c) a five-membered heteroaromatic moiety linked by a nitrogen atom, such as pyrrolyl, pyrazolyl, imidazolyl and triazolyl, which may carry one or two halogen atoms, in particular fluorine and chlorine and/or one or two of the following radicals:

C_1-C_4-alkyl such as methyl, ethyl, 1-propyl, 2-propyl, 2-methyl-2-propyl, 2-methyl-1-propyl, 1-butyl, 2-butyl;

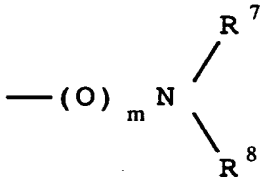
C_1-C_4-haloalkyl, in particular C_1-C_2-haloalkyl such as fluoromethyl, difluoromethyl, trifluoromethyl, chlorodifluoromethyl, dichlorofluoromethyl, trichloromethyl, 1-fluoroethyl, 2-fluoroethyl, 2,2-difluoroethyl, 2,2,2-trifluoroethyl, 2-chloro-2,2-difluoroethyl, 2,2-dichloro-2-fluoroethyl, 2,2,2-trichloroethyl and pentafluoroethyl;

C_1-C_4-haloalkoxy, in particular C_1-C_2-haloalkoxy such as difluoromethoxy, trifluoromethoxy, chlorodifluoromethoxy, 1-fluoroethoxy, 2-fluoroethoxy, 2,2-difluoroethoxy, 1,1,2,2-tetrafluoroethoxy, 2,2,2-trifluoroethoxy, 2-chloro-1,1,2-trifluoroethoxy and pentafluoroethoxy, in particular trifluoromethoxy;

C_1-C_4-alkoxy such as methoxy, ethoxy, propoxy, 1-methylethoxy, butoxy, 1-methylpropoxy, 2-methylpropoxy, 1,1-dimethylethoxy, in particular methoxy, ethoxy, 1-methylethoxy;

C_1-C_4-alkylthio such as methylthio, ethylthio, propylthio, 1-methylethylthio, butylthio, 1-methylpropylthio, 2-methylpropylthio, 1,1-dimethylethylthio, in particular methylthio and ethylthio;

d) R^1 furthermore a radical



where m is 0 or 1 and R^7 and R^8, which can be identical or different, have the following meanings:

hydrogen

C_1-C_8-alkyl, in particular C_1-C_4-alkyl as mentioned above;

C_3-C_6-alkenyl such as 2-propenyl, 2-butenyl, 3-butenyl, 1-methyl-2-propenyl, 2-methyl-2-propenyl, 2-pentenyl, 3-pentenyl, 4-pentenyl, 1-methyl-2-butenyl, 2-methyl-2-butenyl, 3-methyl-2-butenyl, 1-methyl-3-butenyl, 2-methyl-3-butenyl, 3-methyl-3-butenyl, 1,1-dimethyl-2-propenyl, 1,2-dimethyl-2-propenyl, 1-ethyl-2-propenyl, 2-hexenyl, 3-hexenyl, 4-hexenyl, 5-hexenyl, 1-methyl-2-pentenyl, 2-methyl-2-pentenyl, 3-methyl-2-pentenyl, 4-methyl-2-pentenyl, 3-methyl-3-pentenyl, 4-methyl-3-pentenyl, 1-methyl-4-pentenyl, 2-methyl-4-pentenyl, 3-methyl-4-pentenyl, 4-methyl-4-pentenyl, 1,1-dimethyl-2-butenyl, 1,1-dimethyl-3-butenyl, 1,2-dimethyl-2-butenyl, 1,2-dimethyl-3-butenyl, 1,3-dimethyl-2-butenyl, 1,3-dimethyl-3-butenyl, 2,2-dimethyl-3-butenyl, 2,3-dimethyl-2-butenyl, 2,3-dimethyl-3-butenyl, 1-ethyl-2-butenyl, 1-ethyl-3-butenyl, 2-ethyl-2-butenyl, 2-ethyl-3-butenyl, 1,1,2-trimethyl-2-propenyl, 1-ethyl-1-methyl-2-propenyl and 1-ethyl-2-methyl-2-propenyl,

in particular 2-propenyl, 2-butenyl, 3-methyl-2-butenyl and 3-methyl-2-pentenyl;

C_3-C_6-alkynyl such as 2-propynyl, 2-butynyl, 3-butynyl, 1-methyl-2-propynyl, 2-pentynyl, 3-pentynyl, 4-pentynyl, 1-methyl-3-butynyl, 2-methyl-3-butynyl, 1-methyl-2-butynyl, 1,1-dimethyl-2-propynyl, 1-ethyl-2-propynyl, 2-hexynyl, 3-hexynyl, 4-hexynyl, 5-hexynyl, 1-methyl-2-pentynyl, 1-methyl-2-pentynyl, 1-methyl-3-pentynyl, 1-methyl-4-pentynyl, 2-methyl-3-pentynyl, 2-methyl-4-pentynyl, 3-methyl-4-pentynyl, 4-methyl-2-pentynyl, 1,1-dimethyl-2-butynyl, 1,1-dimethyl-3-butynyl, 1,2-dimethyl-3-butynyl, 2,2-dimethyl-3-butynyl, 1-ethyl-2-butynyl, 1-ethyl-3-butynyl, 2-ethyl-3-butynyl and 1-ethyl-1-methyl-2-propynyl, preferably 2-propynyl, 2-butynyl, 1-methyl-2-propynyl and 1-methyl-2-butynyl, in particular 2-propynyl

C_3-C_8-cycloalkyl such as cyclopropyl, cyclobutyl, cyclopentyl, cyclohexyl and cycloheptyl, cyclooctyl, where these alkyl, cycloalkyl, alkenyl and alkynyl groups can each carry one to five halogen atoms, in particular fluorine or chlorine and/or one or two of the following groups:

C_1-C_4-alkyl, C_1-C_4-alkoxy, C_1-C_4-alkylthio, C_1-C_4-haloalkoxy as mentioned above, C_3-C_6-alkenyloxy, C_3-C_6-alkenylthio, C_3-C_6-alkynyloxy, C_3-C_6-alkynylthio, where the alkenyl and alkynyl constituents present in these radicals preferably have the abovementioned meanings;

C_1-C_4-alkylcarbonyl such as, in particular, methylcarbonyl, ethylcarbonyl, propylcarbonyl, 1-methylethylcarbonyl, butylcarbonyl, 1-methylpropylcarbonyl, 2-methylpropylcarbonyl, 1,1-dimethylethylcarbonyl;

C_1-C_4-alkoxycarbonyl such as methoxycarbonyl, ethoxycarbonyl, propyloxycarbonyl, 1-methylethoxycarbonyl, butyloxycarbonyl, 1-methylpropyloxycarbonyl, 2-methylpropyloxycarbonyl, 1,1-dimethylethoxycarbonyl;

C_3-C_6-alkenylcarbonyl, C_3-C_6-alkynylcarbonyl, C_3-C_6-alkenyloxycarbonyl and C_3-C_6-alkynyloxycarbonyl, where the alkenyl and alkynyl radicals are preferably defined as detailed above;

phenyl, unsubstituted or substituted one or more times, eg. one to three times, by halogen, nitro, cyano, C_1-C_4-alkyl, C_1-C_4-haloalkyl, C_1-C_4-alkoxy, C_1-C_4-haloalkoxy or C_1-C_4-alkyl-

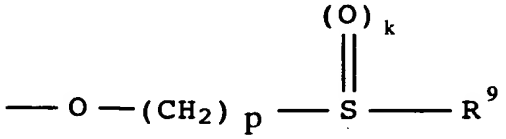
thio, such as 2-fluorophenyl, 3-chlorophenyl, 4-bromophenyl, 2-methylphenyl, 3-nitrophenyl, 4-cyanophenyl, 2-trifluoromethylphenyl, 3-methoxyphenyl, 4-trifluoroethoxyphenyl, 2-methylthiophenyl, 2,4-dichlorophenyl, 2-methoxy-3-methylphenyl, 2,4-dimethoxyphenyl, 2-nitro-5-cyanophenyl, 2,6-difluorophenyl;

di-C_1-C_4-alkylamino such as, in particular, dimethylamino, dipropylamino, N-propyl-N-methylamino, N-propyl-N-ethylamino, diisopropylamino, N-isopropyl-N-methylamino, N-isopropyl-N-ethylamino, N-isopropyl-N-propylamino;

R^7 and R^8 furthermore phenyl which can be substituted by one or more, eg. one to three, of the following radicals: halogen, nitro, cyano, C_1-C_4-alkyl, C_1-C_4-haloalkyl, C_1-C_4-alkoxy, C_1-C_4-haloalkoxy or C_1-C_4-alkylthio, as mentioned above in particular;

or R^7 and R^8 together form a C_4-C_7-alkylene chain which is closed to form a ring, is unsubstituted or substituted, eg. substituted by C_1-C_4-alkyl, and may contain a heteroatom selected from the group consisting of oxygen, sulfur or nitrogen, such as $-(CH_2)_4-$, $-(CH_2)_5-$, $-(CH_2)_6-$, $-(CH_2)_7-$, $-(CH_2)_2-O-(CH_2)_2-$, $-CH_2-S-(CH_2)_3-$, $-(CH_2)_2-O-(CH_2)_3-$, $-NH-(CH_2)_3-$, $-CH_2-NH-(CH_2)_2-$, $-CH_2-CH=CH-CH_2-$, $-CH=CH-(CH_2)_3-$;

e) R^1 furthermore a group



where k is 0, 1 and 2, p is 1, 2, 3 and 4 and R^9 is

C_1-C_4-alkyl, C_1-C_4-haloalkyl, C_3-C_6-alkenyl, C_3-C_6-alkynyl or unsubstituted or substituted phenyl, as mentioned above in particular.

f) R^1 furthermore a radical OR^{10}, where R^{10} is:

hydrogen, the cation of an alkali metal such as lithium, sodium, potassium or the cation of an alkaline earth metal such as calcium, magnesium and barium or an environmentally compatible organic ammonium ion such as tertiary C_1-C_4-alkylammonium or the ammonium ion;

C_3-C_8-cycloalkyl as mentioned above, which may carry one to three C_1-C_4-alkyl groups;

C_1-C_8-alkyl such as, in particular, methyl, ethyl, propyl, 1-methylethyl, butyl, 1-methylpropyl, 2-methylpropyl, 1,1-dimethylethyl, pentyl, 1-methylbutyl, 2-methylbutyl, 3-methylbutyl, 1,2-dimethylpropyl, 1,1-dimethylpropyl, 2,2-dimethylpropyl, 1-ethylpropyl, hexyl, 1-methylpentyl, 2-methylpentyl, 3-methylpentyl, 4-methylpentyl, 1,2-dimethylbutyl, 1,3-dimethylbutyl, 2,3-dimethylbutyl, 1,1-dimethylbutyl, 2,2-dimethylbutyl, 3,3-dimethylbutyl, 1,1,2-trimethylpropyl, 1,2,2-trimethylpropyl, 1-ethylbutyl, 2-ethylbutyl, 1-ethyl-2-methylpropyl, which can carry one to five halogen atoms, in particular fluorine and chlorine and/or one of the following radicals:

C_1-C_4-alkoxy, C_1-C_4-alkylthio, cyano, C_1-C_4-alkylcarbonyl, C_3-C_8-cycloalkyl, C_1-C_4-alkoxycarbonyl, phenyl, phenoxy or phenylcarbonyl, where the aromatic radicals in turn can carry in each case one to five halogen atoms and/or one to three of the following radicals: nitro, cyano, C_1-C_4-alkyl, C_1-C_4-haloalkyl, C_1-C_4-alkoxy, C_1-C_4-haloalkoxy and/or C_1-C_4-alkylthio, as mentioned above in particular;

a C_1-C_8-alkyl as mentioned above, which can carry one to five halogen atoms, in particular fluorine and/or chlorine, and carries one of the following radicals: a 5-membered heteroaromatic moiety containing one to three nitrogen atoms, or a 5-membered heteroaromatic moiety containing a nitrogen atom and an oxygen or sulfur atom, which can carry one to four halogen atoms and/or one or two of the following radicals:

nitro, cyano, C_1-C_4-alkyl, C_1-C_4-haloalkyl, C_1-C_4-alkoxy, phenyl, C_1-C_4-haloalkoxy and/or C_1-C_4-alkylthio. Particular mention may be made of: 1-pyrazolyl, 3-methyl-1-pyrazolyl, 4-methyl-1-pyrazolyl, 3,5-dimethyl-1-pyrazolyl, 3-phenyl-1-pyrazolyl, 4-phenyl-1-pyrazolyl, 4-chloro-1-pyrazolyl, 4-bromo-1-pyrazolyl, 1-imidazolyl, 1-benzimidazolyl, 1,2,4-triazol-1-yl, 3-methyl-1,2,4-triazol-1-yl, 5-methyl-1,2,4-triazol-1-yl, 1-benzotriazolyl, 3-isopropyl-5-isoxazolyl, 3-methyl-5-isoxazolyl, 2-oxazolyl, 2-thiazolyl, 2-imidazolyl, 3-ethyl-5-isoxazolyl, 3-phenyl-5-isoxazolyl, 3-tert-butyl-5-isoxazolyl;

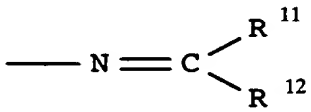
a C_2-C_6-alkyl group which carries one of the following radicals in position 2: C_1-C_4-alkoxyimino, C_3-C_6-alkynyloxyimino, C_3-C_6-haloalkenyloxyimino or benzyloxyimino;

a C_3-C_6-alkenyl or C_3-C_6-alkynyl group, it being possible for these groups in turn to carry one to five halogen atoms;

R^{10} furthermore a phenyl radical which can carry one to five halogen atoms and/or one to three of the following radicals: nitro, cyano, C_1-C_4-alkyl, C_1-C_4-haloalkyl, C_1-C_4-alkoxy, C_1-C_4-haloalkoxy and/or C_1-C_4-alkylthio, as mentioned above in particular;

a 5-membered heteroaromatic moiety which is linked via a nitrogen atom, contains one to three nitrogen atoms and can carry one or two halogen atoms and/or one or two of the following radicals: C_1-C_4-alkyl, C_1-C_4-haloalkyl, C_1-C_4-alkoxy, phenyl, C_1-C_4-haloalkoxy and/or C_1-C_4-alkylthio. Particular mention may be made of: 1-pyrazolyl, 3-methyl-1-pyrazolyl, 4-methyl-1-pyrazolyl, 3,5-dimethyl-1-pyrazolyl, 3-phenyl-1-pyrazolyl, 4-phenyl-1-pyrazolyl, 4-chloro-1-pyrazolyl, 4-bromo-1-pyrazolyl, 1-imidazolyl, 1-benzimidazolyl, 1,2,4-triazol-1-yl, 3-methyl-1,2,4-triazol-1-yl, 5-methyl-1,2,4-triazol-1-yl, 1-benzotriazolyl, 3,4-dichloro-1-imidazolyl;

R^{10} furthermore a group



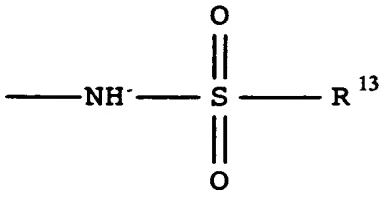
where R^{11} and R^{12}, which can be identical or different, are:

C_1-C_8-alkyl, C_3-C_6-alkenyl, C_3-C_6-alkynyl, C_3-C_8-cycloalkyl, it being possible for these radicals to carry a C_1-C_4-alkoxy, C_1-C_4-alkylthio and/or an unsubstituted or substituted phenyl radical, as mentioned above in particular;

phenyl which can be substituted by one or more, eg. one to three, of the following radicals: halogen, nitro, cyano, C_1-C_4-alkyl, C_1-C_4-haloalkyl, C_1-C_4-alkoxy, C_1-C_4-haloalkoxy or C_1-C_4-alkylthio, where these radicals are, in particular, those mentioned above;

or R^{11} and R^{12} together form a C_3-C_{12}-alkylene chain which can carry one to three C_1-C_4-alkyl groups and contain a heteroatom from the group consisting of oxygen, sulfur and nitrogen, as mentioned in particular for R^7 and R^8.

g) R^1 furthermore a radical



where R^{13} is:

C_1-C_4-alkyl, C_3-C_6-alkenyl, C_3-C_6-alkynyl, C_3-C_8-cycloalkyl as mentioned above in particular, it being possible for these radicals to carry a C_1-C_4-alkoxy, C_1-C_4-alkylthio and/or a phenyl radical as mentioned above;

phenyl, unsubstituted or substituted, in particular as mentioned above.

In respect of the biological effect, preferred carboxylic acid derivatives of the general formula I are those where the substituents have the following meanings:

R^2 the C_1-C_4-alkyl, C_1-C_4-haloalkyl, C_1-C_4-alkoxy, C_1-C_4-haloalkoxy, C_1-C_4-alkylthio groups and halogen atoms mentioned in detail for R^1, especially chlorine, methyl, methoxy, ethoxy, difluoromethoxy, trifluoromethoxy;

X nitrogen or CR^{14} where

R^{14} is hydrogen or alkyl, or CR^{14} forms together with CR^3 a 4- to 5-membered alkylene or alkenylene ring in which, in each case, a methylene group can be replaced by oxygen or sulfur, such as $-CH_2-CH_2-O-$, $-CH=CH-O-$, $-CH_2-CH_2-CH_2-O-$, $-CH=CH-CH_2O-$, in particular hydrogen, $-CH_2-CH_2-O-$, $-CH(CH_3)-CH(CH_3)-O-$, $-C(CH_3)=C(CH_3)-O-$, $-CH=C(CH_3)-O-$ or $-C(CH_3)=C(CH_3)-S$;

R^3 the C_1-C_4-alkyl, C_1-C_4-haloalkyl, C_1-C_4-alkoxy, C_1-C_4-haloalkoxy, C_1-C_4-alkylthio groups and halogen atoms mentioned for R^1, especially chlorine, methyl, methoxy,

ethoxy, difluoromethoxy, trifluoromethoxy or is linked to R^{14} as mentioned above to give a 5- or 6-membered ring;

R^4 and R^5 phenyl or naphthyl, which can be substituted by one or more, eg. one to three, of the following radicals: halogen, nitro, cyano, hydroxyl, mercapto, amino, C_1-C_4-alkyl, C_1-C_4-haloalkyl, C_1-C_4-alkoxy, C_1-C_4-haloalkoxy, C_1-C_4-alkylthio, C_1-C_4-alkylamino, di-C_1-C_4-alkylamino, C_1-C_4-alkylcarbonyl, C_1-C_4-alkoxycarbonyl; phenyl or naphthyl, which are connected together in the ortho positions by a direct linkage, a methylene, ethylene or ethenylene group, an oxygen or sulfur atom or an SO_2, NH or N-alkyl group;

R^6 C_1-C_8-alkyl, C_3-C_6-alkenyl, C_3-C_6-alkynyl or C_3-C_8-cycloalkyl as mentioned above in particular, it being possible for these radicals in each case to be substituted one or more times by: halogen, hydroxyl, nitro, cyano, C_1-C_4-alkoxy, C_3-C_6-alkenyloxy, C_3-C_6-alkynyloxy, C_1-C_4-alkylthio, C_1-C_4-haloalkoxy, C_1-C_4-alkylcarbonyl, hydroxycarbonyl, C_1-C_4-alkoxycarbonyl, C_1-C_4-alkylamino, di-C_1-C_4-alkylamino or unsubstituted or substituted phenyl or phenoxy, as mentioned above in particular;

phenyl or naphthyl, which can be substituted by one or more of the following radicals: halogen, nitro, cyano, hydroxyl, amino, C_1-C_4-alkyl, C_1-C_4-haloalkyl, C_1-C_4-alkoxy, C_1-C_4-haloalkoxy, phenoxy, C_1-C_4-alkylthio, C_1-C_4-akylamino [sic] or C_1-C_4-dialkylamino, as mentioned in particular for R^7 and R^4;

a five- or six-membered heteroaromatic moiety which contains one to three nitrogen atoms and/or one sulfur or oxygen atom and which can carry one to four halogen atoms and/or one or two of the following radicals: C_1-C_4-alkyl, C_1-C_4-haloalkyl, C_1-C_4-alkoxy, C_1-C_4-haloalkoxy, C_1-C_4-alkylthio, phenyl, phenoxy or phenylcarbonyl, it being possible for the phenyl radicals in turn to carry one to five halogen atoms and/or one to three of the following radicals: C_1-C_4-alkyl, C_1-C_4-haloalkyl, C_1-C_4-alkoxy, C_1-C_4-haloalkoxy and/or C_1-C_4-alkylthio, as mentioned for R^4 in particular;

Y sulfur, oxygen or a single bond;

Z sulfur or oxygen or a single bond.

Particularly preferred compounds of the formula I are those in which the substituents have the following meanings:

R^2 C_1-C_4-alkyl, C_1-C_4-alkoxy

X nitrogen or CR^{14}, where

R^{14} is hydrogen or alkyl, or CR^{14} forms together with CR^3 a 4- or 5-membered alkylene or alkenylene ring in which in each case a methylene group can be replaced by oxygen or sulfur, such as $-CH_2-CH_2-O-$, $-CH=CH-O-$, $-CH_2-CH_2-CH_2-O-$, $-CH=CH-CH_2O-$, in particular hydrogen, $-CH_2-CH_2-O-$, $-CH(CH_3)-CH(CH_3)-O-$, $-C(CH_3)=C(CH_3)-O-$, $-CH=C(CH_3)-O-$ or $-C(CH_3)=C(CH_3)-S$;

R^3 the C_1-C_4-alkyl, C_1-C_4-alkoxy, C_1-C_4-alkylthio groups mentioned for R^1, or is linked to R^{14} as mentioned above to give a 5- or 6-membered ring;

R^4 and R^5 phenyl (identical or different) which can be substituted by one or more, eg. one to three, of the following radicals: halogen, nitro, hydroxyl, C_1-C_4-alkyl, C_1-C_4-alkoxy, C_1-C_4-alkylthio or

R^4 and R^5 are phenyl groups which are connected together in the ortho positions by a direct linkage, a methylene, ethylene or ethenylene group, an oxygen or sulfur atom or an SO_2, NH or N-alkyl group;

R^6 C_1-C_8-alkyl, C_3-C_6-alkenyl or C_3-C_8-cycloalkyl, it being possible for these radicals in each case to be substituted one or more times by: halogen, hydroxyl, nitro, cyano, C_1-C_4-alkoxy, C_3-C_6-alkenyloxy, C_1-C_4-alkylthio;

phenyl or naphthyl, which can be substituted by one or more of the following radicals: halogen, nitro, cyano, hydroxyl, amino, C_1-C_4-alkyl, C_1-C_4-haloalkyl, C_1-C_4-alkoxy, C_1-C_4-haloalkoxy, phenoxy, C_1-C_4-alkylthio, C_1-C_4-akylamino [sic] or C_1-C_4-dialkylamino;

a five- or six-membered heteroaromatic moiety which contains a nitrogen atom and/or a sulfur or oxygen atom and which can carry one to four halogen atoms and/or one or two of the following radicals: C_1-C_4-alkyl, C_1-C_4-haloalkyl, C_1-C_4-alkoxy, C_1-C_4-alkylthio, phenyl, phenoxy or phenylcarbonyl, it being possible for the phenyl radicals in turn to carry one to five halogen atoms and/or one to three of the following radicals:

C_1-C_4-alkyl, C_1-C_4-haloalkyl, C_1-C_4-alkoxy and/or C_1-C_4-alkylthio;

Y sulfur, oxygen or a single bond;

Z sulfur or oxygen or a single bond.

Examples of preferred compounds are linked in the table below:

Table 1: Compounds of the formula I, R = -CO-R^1

R^1	R^4, R^5	R^6	R^2	R^3	X	Y	Z
OH	Phenyl	Methyl	OCH_3	OCH_3	CH	S	S
OH	Phenyl	Methyl	OCH_3	OCH_3	CH	O	S
OCH_3	Phenyl	Methyl	OCH_3	OCH_3	CH	S	S
OH	Phenyl	Methyl	OCH_3	OCH_3	CH	O	O
OCH_3	2-Fluorophenyl	Methyl	OCH_3	OCH_3	CH	O	O
OC_2H_5	3-Chlorophenyl	Methyl	OCH_3	OCH_3	N	O	O
$ON(CH_3)_2$	4-Bromophenyl	Methyl	CF_3	CF_3	CH	S	O
$O-CH_2-C\equiv CH$	Phenyl	Ethyl	OCH_3	CF_3	CH	O	O
OH	Phenyl	Propyl	OCH_3	OCF_3	CH	O	S
OCH_3	Phenyl	i-Propyl	OCH_3	CH_3	CH	O	O
OC_2H_5	Phenyl	s-Butyl	OCH_3	Cl	CH	S	O
$ON(CH_3)_2$	2-Methylphenyl	Methyl	OCH_3	OCH_3	CH	O	O
$ON(CH_3)_2$	3-Methoxyphenyl	Methyl	OCH_3	OCH_3	CH	O	O
$ON=C(CH_3)_2$	4-Nitrophenyl	Methyl	OCH_3	OCH_3	CH	O	O
$ON(CH_3)_2$	Phenyl	1-Phenylpropyn-3-yl	OCH_3	OCF_3	N	O	S
$ON=C(CH_3)_2$	2-Hydroxyphenyl	Methyl	OCH_3	CH_3	N	O	O
$ONSO_2C_6H_5$	3-Trifluoromethylphenyl	Methyl	OCH_3	Cl	N	O	O
NHPhenyl	4-Dimethylaminophenyl	Methyl	OCH_3	OCH_3	CH	S	O
OC_2H_5	Phenyl	Trifluoroethyl	CH_3	CH_3	CH	O	O

R^1	R^4, R^5	R^6	R^2	R^3	X	Y	Z
$ON(CH_3)_2$	Phenyl	Benzyl	Cl	Cl	CH	O	O
$ON(CH_3)_2$	Phenyl	2-Methoxyethyl	OCH_3	$-O-CH_2-CH_2-$		S	O
OH	Phenyl	Phenyl	OCH_3	OCH_3	CH	O	O
OH	Phenyl	Phenyl	OCH_3	$-O-CH_2-CH_2-$		O	O
OH	Phenyl	Phenyl	OCH_3	OCH_3	N	O	O
OH	Phenyl	Phenyl	OCH_3	OCH_3	CH	S	O
OH	Phenyl	Phenyl	OCH_3	OCH_3	CH	S	S
OH	Phenyl	Phenyl	OCH_3	OCH_3	CH	O	S
OH	Phenyl	Phenyl	OCH_3	OCH_3	CH	O	O
OH	Phenyl	Phenyl	OCH_3	OCH_3	CH	O	O
OH	Phenyl	2-Thiazolyl	OCH_3	OCH_3	CH	O	O
OCH_3	2-Fluorophenyl	Phenyl	OCH_3	OCH_3	CH	O	O
OC_2H_5	3-Chlorophenyl	Phenyl	OCH_3	OCH_3	N	O	O
$ON(CH_3)_2$	4-Bromophenyl	Phenyl	CF_3	CF_3	CH	S	O
$O-CH_2{\equiv}CH$	Phenyl	2-Fluorophenyl	OCH_3	CF_3	CH	O	O
OH	Phenyl	3-Chlorophenyl	OCH_3	OCF_3	CH	O	S
OCH_3	Phenyl	4-Bromophenyl	OCH_3	CH_3	CH	O	O
OC_2H_5	Phenyl	4-Thiazolyl	OCH_3	Cl	CH	S	O
$ON(CH_3)_2$	2-Methylphenyl	Phenyl	OCH_3	OCH_3	CH	O	O
$ON{=}C(CH_3)_2$	3-Methoxyphenyl	Phenyl	OCH_3	OCH_3	CH	O	O
$NH-SO-C_6H_5$	4-Nitrophenyl	Phenyl	OCH_3	OCH_3	CH	O	O

R^1	R^4, R^5	R^6	R^2	R^3	X	Y	Z
OCH_3	Phenyl	3-Imidazolyl	OCH_3	$-O-CH_2-CH_2-$		O	O
OC_2H_5	Phenyl	4-Imidazolyl	OCH_3	CF_3	N	S	O
$ON(CH_3)_2$	Phenyl	2-Pyrazolyl	OCH_3	OCF_3	N	O	S
$ON=C(CH_3)_2$	2-Hydroxyphenyl	Phenyl	OCH_3	CH_3	N	O	O
$NH-SO_2-C_6H_5$	3-Trifluoromethylphenyl	Phenyl	OCH_3	Cl	N	O	O
NHPhenyl	4-Dimethylaminophenyl	Phenyl	OCH_3	OCH_3	CH	S	O
OC_2H_5	Phenyl	2-Dimethylaminophenyl	CH_3	CH_3	CH	O	O
$ON(CH_3)_2$	Phenyl	3-Hydroxyphenyl	Cl	Cl	CH	O	O
$ON=C(CH_3)_2$	Phenyl	4-Trifluoromethylphenyl	OCH_3	$-O-CH_2-CH_2-$		S	O
$NH-SO_2-C_6H_5$	Phenyl	2-Oxazolyl	OCH_3	CF_3	N	S	S

The compounds of the present invention provide a novel therapeutic potential for the treatment of hypertension, pulmonary hypertension, myocardial infarct, angina pectoris, acute kidney failure, renal insufficiency, cerebral vasospasms, cerebral ischemia, subarachnoid hemorrhages, migraine, asthma, atherosclerosis, endotoxic shock, endotoxin-induced organ failure, intravascular coagulation, restenosis after angioplasty, benign prostate hyperplasia, or hypertension or kidney failure caused by ischemia or intoxication.

The good effect of the compounds can be shown in the following tests:

Receptor binding studies

Cloned human ET_A receptor-expressing CHO cells and guinea pig cerebellar membranes with > 60 % ET_B compared with ET_A receptors were used for binding studies.

Membrane preparation

The ET_A receptor-expressing CHO cells were grown in F_{12} medium containing 10 % fetal calf serum, 1 % glutamine, 100 U/ml penicillin and 0.2 % streptomycin (Gibco BRL, Gaithersburg, MD, USA). After 48 h, the cells were washed with PBS and incubated with 0.05 % trypsin-containing PBS for 5 min. Neutralization was then carried out with F_{12} medium, and the cells were collected by centrifugation at 300 x g. To lyze the cells, the pellet was briefly washed with lysis buffer (5 mM Tris-HCl, pH 7.4 with 10 % glycerol) and then incubated at a concentration of 10^7 cells/ml of lysis buffer at 4°C for 30 min. The membranes were centrifuged at 20,000 x g for 10 min, and the pellet was stored in liquid nitrogen.

Guinea pig cerebella were homogenized in a Potter-Elvejhem homogenizer and [lacuna] obtained by differential centrifugation at 1000 x g for 10 min and repeated centrifugation of the supernatant at 20,000 x g for 10 min.

Binding assays

For the ET_A and ET_B receptor binding assay, the membranes were suspended in incubation buffer (50 mM Tris-HCl, pH 7.4 with 5 mM $MnCl_2$, 40 µg/ml bacitracin and 0.2 % BSA) at a concentration of 50 µg of protein per assay mixture and incubated with 25 pM [125I [sic]]-ET_1 (ET_A receptor assay) or 25 pM [125I [sic]]-RZ_3 (ET_B receptor assay) in the presence and absence of test substance at

25°C. The nonspecific binding was determined using 10^{-7} M ET_1. After 30 min, the free and bound radioligand were separated by filtration through GF/B glass fiber filters (Whatman, England) on a Skatron cell collector (Skatron, Lier, Norway) and the filters were washed with ice-cold Tris-HCl buffer, pH 7.4 with 0.2 % BSA. The radioactivity collected on the filters was quantified using a Packard 2200 CA liquid scintillation counter.

Functional in vitro assay system to look for endothelin receptor (subtype A) antagonists

This assay system is a functional, cell-based assay for endothelin receptors. When certain cells are stimulated with endothelin 1 (ET1) they show an increase in the intracellular calcium concentration. This increase can be measured in intact cells loaded with calcium-sensitive dyes.

1-Fibroblasts which had been isolated from rats and in which an endogenous endothelin receptor of the A subtype had been detected were loaded with the fluorescent dye Fura 2-an as follows: after trypsinization, the cells were resuspended in buffer A (120 mM NaCl, 5 mM KCl, 1.5 mM $MgCl_2$, 1 mM $CaCl_2$, 25 mM HEPES, 10 mM glucose, pH 7.4) to a density of 2 x 10^6/ml and incubated with Fura 2-am (2 µM), Pluronics F-127 (0.04 %) und DMSO (0.2 %) at 37°C in the dark for 30 min. The cells were then washed twice with buffer A and resuspended at 2 x 10^6/ml.

The fluorescence signal from 2 x 10^5 cells per ml with Ex/Em 380/510 was recorded continuously at 30°C. To the cells were the test substances and, after an incubation time of 3 min, ET1 was and the maximum change in the fluorescence determined. [sic] The response of the cells to ET1 without previous addition of a test substance was used as control and was set equal to 100 %.

Testing of ET antagonists in vivo

Male SD rats weighting 250-300 g were anesthetized with amobarbital, artifically ventilated, vagotomized and pithed. The carotid artery and jugular vein were catheterized.

In control animals, intravenous administration of 1 µg/kg ET1 leads to a distinct rise in blood [sic] which persists for a lengthy period.

The test animals received an i.v. injection of the test compounds (1 ml/kg) 5 min before the administration of ET1. To determine the ET-antagonistic properties, the rise in blood pressure in the test animals was compared with that in the control animals.

Endothelin-1-induced sudden death in mice

The principle of the test is the inhibition of the sudden heart death caused in mice by endothelin, which is probably induced by constriction of the coronary vessels, by pretreatment with endothelin receptor antagonists. Intravenous injection of 10 nmol/kg endothelin in a volume of 5 ml/kg of body weight results in death of the animals within a few minutes.

The lethal endothelin-1 dose is checked in each case on a small group of animals. If the test substance is administered intravenously, the endothelin-1 injection which was lethal in the reference group usually takes place 5 min thereafter. With other modes of administration, the times before administration are extended, where appropriate up to several hours.

The survival rate is recorded, and effective doses which protect 50 % of the animals (ED 50) from endothelin-induced heart death for 24 h or longer are determined.

Functional test on vessels for endothelin receptor antagonists

Segments of rabbit aorta are, after an initial tension of 2 g and a relaxation time of 1 h in Krebs-Henseleit solution at 37°C and pH 7.3-7.4, first induced to contract with K^+. After washing out, an endothelin dose-effect plot up to the maximum is constructed.

Potential endothelin antagonists are administered to other preparations of the same vessel 15 min before starting the endothelin dose-effect plot. The effects of the endothelin are calibrated as a % of the K^+-induced contraction. Effective endothelin antagonists result in a shift to the right in the endothelin dose-effect plot.

The compounds according to the invention can be administered orally or parenterally (subcutaneously, intravenously, intramuscularly, intraperotoneally [sic]) in a conventional way. Administration can also take place with vapors or sprays through the nasopharyngeal space.

The dosage depends on the age, condition and weight of the patient and on the mode of administration. The daily dose of active substance is, as a rule, about 0.5-50 mg/kg of body weight on oral administration and about 0.1-10 mg/kg of body weight on parenteral administration.

The novel compounds can be used in conventional solid or liquid pharmaceutical forms, eg. as uncoated or (film-)coated tablets, capsules, powders, granules, suppositories, solutions, ointments, creams or sprays. These are produced in a conventional way. The active substances can for this purpose be processed with conventional pharmaceutical aids such as tablet binders, fillers, preservatives, tablet disintegrants, flow regulators, plasticizers, wetting agents, dispersants, emulsifiers, solvents, release-slowing agents, antioxidants and/or propellent gases (cf. H. Sucker et al.: Pharmazeutische Technologie, Thieme-Verlag, Stuttgart, 1991). The administration forms obtained in this way normally contain from 0.1 to 90 % by weight of the active substance.

Synthesis examples

Example 1
Methyl 2-hydroxy-3-methoxy-3,3-diphenylpropionate

5 g (19.6 mmol) of methyl 3,3-diphenyl-2,3-epoxypropionate were dissolved in 50 ml of absolute methanol and, at 0°C, 0.1 ml of boron trifluoride etherate was added. The mixture was stirred at 0°C for 2 h and at room temperature for a further 12 h. The solvent was distilled out, the residue was taken up in ethyl acetate, washed with sodium bicarbonate solution and water and dried over magnesium sulfate. After removal of the solvent by distillation there remained 5.5 g (88 %) of a pale yellow oil.

Example 2
Methyl 2-hydroxy-3-phenoxy-3,3-diphenylpropionate

5 g (19.6 mmol) of methyl 3,3-diphenyl-2,3-epoxypropionate and 5.6 g (60 mmol) of phenol were heated together at 100°C for 6 h. Removal of the excess phenol by distillation under high vacuum and purification of the residue by chromatography on silica gel with hexane/ethyl acetate mixtures resulted in 4.9 g (77 %) of a pale yellow oil.

Example 3
Methyl 2-(4,6-dimethoxy-pyrimidin-2-yloxy)-3-methoxy-3,3-diphenylpropionate

2.86 g (10 mmol) of methyl 2-hydroxy-3-methoxy-3,3-diphenylpropionate were dissolved in 40 ml of dimethylformamide, and 0.3 g (12 mmol) of sodium hydride was added. The mixture was stirred for 1 h and then 2.2 g (10 mmol) of 4,6-dimethoxy-2-methylsulfonylpyrimidine were added. After stirring at room temperature for 24 h, cautious hydrolysis was carried out with 10 ml of water, the pH was adjusted to 5 with acetic acid, and the solvent was removed by distillation under high vacuum. The residue was taken up in 100 ml of ethyl acetate, washed with water and dried over magnesium sulfate, and the solvent was distilled out. The residue was mixed with 10 ml of ether, and the resulting precipitate was filtered off with suction. After drying, 3.48 g (82 %) of a white powder remained.
Melting point 81°C.

Example 4
2-(4,6-Dimethoxy-pyrimidin-2-yloxy)-3-methoxy-3,3-diphenylpropionic acid

2.12 g (5 mmol) of methyl 2-(4,6-dimethoxy-pyrimidin-2-yloxy)-3-methoxy-3,3-diphenylpropionate were dissolved in 50 ml of dioxane, 10 ml of 1 N KOH solution were added, and the mixture was stirred at 100°C for 3 h. The solution was diluted with 300 ml of water and extracted with ethyl acetate to remove unreacted ester. The aqueous phase was then adjusted to pH 1-2 with dilute hydrochloric acid and extracted with ethyl acetate. After drying over magnesium sulfate and removal of the solvent by distillation, the residue was mixed with an ether/hexane mixture, and the precipitate which formed was filtered off with suction. After drying, 1.85 g (90 %) of a white powder remained.
Melting point 167°C

Example 5
Methyl 2-[(4,6-dimethoxypyrimidin-2-yl)thio]-3-methoxy-3,3-diphenylpropionate [sic]

7.16 g (25 mmol) of methyl 2-hydroxy-3-methoxy-3,3-diphenylpropionate were dissolved in 50 ml of dichloromethane, 3 g (30 mmol) of triethylamine were added, and 3.2 g (28 mmol) of methanesulfonyl chloride were added dropwise while stirring. The mixture was stirred at room temperature for 2 h, washed with water, dried over magnesium sulfate and concentrated under reduced pressure. The residue was taken up in DMF and added dropwise at 0°C to a

suspension of 12.9 g (75 mmol) of 4,6-dimethoxypyrimidine-2-thiol and 8.4 g (100 mmol) of sodium bicarbonate in 100 ml of DMF. After stirring at room temperature for 2 h and at 60°C for a further 2 h, the mixture was poured into 1 liter of ice-water, and the resulting precipitate was filtered off with suction. After drying, 3.19 g (29 %) of a white powder remained.

Example 6
Methyl 2-benzhydrylideneamino-3,3-diphenylpropionate

10.65 g (42 mmol) of N-(diphenylmethylene)glycine methyl ester were introduced into 100 ml of absolute tetrahydrofuran under nitrogen. At -78°C, 31.5 ml (63 mmol) of a 2 molar lithium diisopropylamide solution in tetrahydrofuran were added dropwise, and the mixture was stirred for 1 h. To this solution were added dropwise 12.5 g (50 mmol) of bromodiphenylmethane dissolved in 50 ml of absolute tetrahydrofuran, at -78°C, followed by stirring for 2 h. Water was added to the solution, the tetrahydrofuran was evaporated off under reduced pressure, the aqueous phase was extracted with ethyl acetate and dried over magnesium sulfate. The crude product was purified by chromatography on silica gel with hexane/ethyl acetate mixtures, and 5.25 g (30 %) of a pale yellow oil were obtained.

Example 7
Methyl 2-amino-3,3-diphenylpropionate

5.25 g (12.5 mmol) of methyl 2-benzhydrylideneamino-3,3-diphenylpropionate were dissolved in 160 ml of tetrahydrofuran, 30 ml of dilute hydrochloric acid were added and the mixture was stirred for 90 min. Tetrahydrofuran was evaporated off under reduced pressure and the impuritites were extracted with ethyl acetate. The aqueous phase was made alkaline with 5 % strength ammonia solution and extracted with ethyl acetate. The organic phase was dried over magnesium sulfate and then evaporated under reduced pressure. 2.84 g (89 %) of a yellow oil were obtained.

Example 8
Methyl 2-hydroxy-3,3-diphenylpropionate

2.07 g (8.1 mmol) of methyl 2-amino-3,3-diphenylpropionate were dissolved in 30 ml of 0.5 molar sulfuric acid at 0°C. To this were added dropwise 1.8 g (25.7 mmol) of sodium nitrite dissolved in 15 ml of water, followed by stirring for 1 h. The solution was extracted with ethyl acetate, and the organic phase was washed with sodium bicarbonate solution and dried over magnesium sulfate. The residue after evaporation under reduced pressure was

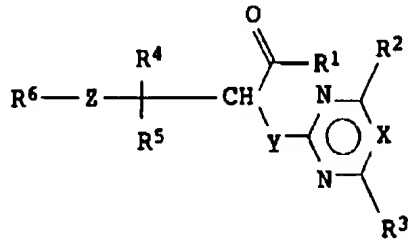
purified by chromatography on silica gel with cyclohexane/ethyl acetate mixtures, and 1.16 g (56 %) of a white solid were obtained.

Example 9
Methyl 2-hydroxy-3,3-diphenylbutyrate

1.5 g (5.9 mmol) of methyl 3,3-diphenyl-2,3-epoxypropionate dissolved in 10 ml of absolute ether were added dropwise to a cuprate solution which had been prepared from 635 mg (7 mmol) of copper(I) cyanide dissolved in 10 ml of absolute ether and 8.14 ml (13 mmol) of a 1.6 normal methyllithium solution and had been cooled to -78°C. The solution was stirred at -78°C for 1 h and then allowed to warm to room temperature. It was subsequently diluted with 100 ml of ether and 100 ml of water, and the ether phase was washed with dilute citric acid and with sodium bicarbonate solution and dried over magnesium sulfate. The crude product was purified by chromatography on silica gel with cyclohexane/ethyl acetate mixtures to result in 250 mg (16 %) of a pale yellow oil.

The compounds mentioned in Table 1 can be prepared in a similar manner.

Table



No.	R^1	R^4	R^5	R^6	R^2	R^3	X	Y	Z	m.p.[°C]
10	OMe	Phenyl	Phenyl	Methyl	OMe	OMe	CH	O	O	81
11	OH	Phenyl	Phenyl	Methyl	OMe	OMe	CH	O	O	167
12	OH	Phenyl	Phenyl	CH_2-CH_2-S-CH_3	OMe	OMe	CH	O	O	
13	OH	Phenyl	Phenyl	Ethyl	OMe	OMe	CH	O	O	87 (dccomp.)
14	OH	Phenyl	Phenyl	iso-Propyl	OMe	OMe	CH	O	O	182
15	OH	Phenyl	Phenyl	Methyl	OMe	OMe	CH	O	S	
16	OH	Phenyl	Phenyl	CH_2-CH_2-SO_2-$CH(CH_3)_2$	OMe	OMe	CH	O	O	
17	OH	Phenyl	Phenyl	CH_2-CH_2-SO_2-$CH(CH_3)_2$	OMe	OMe	CH	S	O	
18	OH	Phenyl	Phenyl	CH_2-CH_2-SO_2-$CH(CH_3)_2$	OMe	OMe	C-$CH(CH_3)_2$	O	O	

No.	R^1	R^4	R^5	R^6	R^2	R^3	X	Y	Z	m.p.[°C]
19	OH	Phenyl	Phenyl	CH_2-CH_2-SO_2-$CH(CH_3)_2$	OMe	OMe	C-$CH(CH_3)_3$	O	O	
20	OH	Phenyl	Phenyl	CH_2-CH_2-SO_2-$CH(CH_3)_2$	OMe	NH-OCH_3	CH	O	O	
21	OH	Phenyl	Phenyl	n-Propyl	OMe	OMe	CH	O	O	174
22	OMe	Phenyl	Phenyl	n-Propyl	OMe	OMe	CH	O	O	
23	OH	Phenyl	Phenyl	n-Propyl	OEt	OEt	CH	O	O	
24	OH	Phenyl	Phenyl	n-Butyl	OMe	OMe	CH	O	O	
25	OH	Phenyl	Phenyl	iso-Butyl	OMe	OMe	CH	O	O	
26	OH	Phenyl	Phenyl	iso-Butyl	OMe	O-CH_2-CH_2-C		O	O	
27	OH	Phenyl	Phenyl	tert.-Butyl	OMe	OMe	CH	O	O	
28	OH	Phenyl	Phenyl	Cyclopropyl	OMe	OMe	CH	O	O	
29	OH	Phenyl	Phenyl	Cyclopentyl	OMe	OMe	CH	O	O	
30	OH	Phenyl	Phenyl	Cyclohexyl	OMe	OMe	CH	O	O	
31	OH	Phenyl	Phenyl	$(CH_3)_3C$-CH_2-CH_2	OEt	OEt	CH	O	O	
32	OH	Phenyl	Phenyl	$(CH_3)_2CH$-CH_2-CH_2-CH_2	OMe	OMe	CH	O	O	173
33	OH	Phenyl	Phenyl	HO-CH_2-CH_2	OMe	OMe	CH	O	O	
34	OH	Phenyl	Phenyl	HO_2C-$(CH_2)_2$-	OMe	OMe	CH	O	O	
35	OH	Phenyl	Phenyl	Cyclopro-pylmethylene	OMe	OMe	CH	O	O	115
36	OH	Phenyl	Phenyl	H	OMe	OMe	CH	O	O	

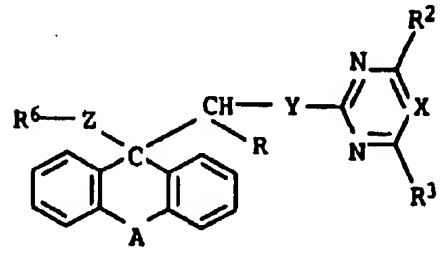
No.	R^1	R^4	R^5	R^6	R^2	R^3	X	Y	Z	m.p.[°C]
37	OH	Phenyl	Phenyl	Methyl	OMe	OMe	CH	O	-	
38	OH	Phenyl	Phenyl	Phenyl	OMe	OMe	CH	O	O	136
39	OH	Phenyl	Phenyl	Phenyl	OMe	O-CH(CH_3)-CH_2-C		O	O	
40	OMe	Phenyl	Phenyl	Phenyl	OMe	OMe	CH	O	O	
41	OH	Phenyl	Phenyl	p-Isopropylphenyl	OMe	OMe	CH	O	O	
42	OH	Phenyl	Phenyl	p-Me-S-Phenyl	OMe	OMe	CH	O	O	
43	OH	Phenyl	Phenyl	p-Me-O-Phenyl	OMe	OMe	CH	O	O	
44	OH	Phenyl	Phenyl	m-Et-Phenyl	OMe	OMe	CH	O	O	
45	OH	Phenyl	Phenyl	o-Me-Phenyl	OMe	OMe	CH	O	O	
46	OH	Phenyl	Phenyl	o-Cl-Phenyl	OMe	OMe	CH	O	O	
47	OH	Phenyl	Phenyl	m-Br-Phenyl	OMe	OMe	CH	O	O	
48	OH	Phenyl	Phenyl	p-F-Phenyl	OMe	OMe	CH	O	O	
49	OH	Phenyl	Phenyl	p-F-Phenyl	OMe	OMe	CH	S	O	
50	OH	Phenyl	Phenyl	p-CH_3-Phenyl	OMe	OMe	CH	O	O	
51	OH	Phenyl	Phenyl	m-NO_2-Phenyl	OMe	OMe	CH	O	O	
52	OH	Phenyl	Phenyl	O-HO-Phenyl	OMe	OMe	CH	O	O	

No.	R^1	R^4	R^5	R^6	R^2	R^3	X	Y	Z	m.p.[°C]
53	OH	Phenyl	Phenyl	3,4-Dimethoxy-Phenyl	OMe	OMe	CH	O	O	
54	OH	Phenyl	Phenyl	3,4-Dioxomethylene-phenyl	OMe	OMe	CH	O	O	
55	OH	Phenyl	Phenyl	3,4,5-Trimethoxy-phenyl	OMe	OMe	CH	O	O	
56	OH	Phenyl	Phenyl	Benzyl	OMe	OMe	CH	O	O	
57	OH	Phenyl	Phenyl	o-Cl-Benzyl	OMe	OMe	CH	O	O	
58	OH	Phenyl	Phenyl	m-Br-Benzyl	OMe	OMe	CH	O	O	
59	OH	Phenyl	Phenyl	p-F-Benzyl	OMe	OMe	CH	O	O	
60	OH	Phenyl	Phenyl	o-Me-Benzyl	OMe	OMe	CH	O	O	
61	OH	Phenyl	Phenyl	o-Me-Benzyl	OMe	O-CH=CH-C		O	O	
62	OH	Phenyl	Phenyl	m-Et-Benzyl	OMe	OMe	CH	O	O	
63	OH	Phenyl	Phenyl	p-iso-Propyl-Benzyl	OMe	OMe	CH	O	O	
64	OH	Phenyl	Phenyl	p-NO_2-Propyl-Benzyl	OMe	OMe	CH	O	O	
65	OH	Phenyl	Phenyl	o-Me-O-Propyl-Benzyl	OMe	OMe	CH	O	O	
66	OH	Phenyl	Phenyl	o-Me-O-Propyl-Benzyl	OEt	OEt	CH	O	O	

No.	R^1	R^4	R^5	R^6	R^2	R^3	X	Y	Z	m.p.[°C]
67	OH	Phenyl	Phenyl	p-Me-O-Propyl-Benzyl	OMe	OMe	CH	O	O	
68	OH	Phenyl	Phenyl	3,4-Dioxomethylene-benzyl [sic]	OMe	OMe	CH	O	O	
69	OH	p-F-Phenyl	p-F-Phenyl	Methyl	OMe	OMe	CH	O	O	
70	OMe	p-F-Phenyl	p-F-Phenyl	Methyl	OEt	OEt	CH	O	O	
71	OH	p-Cl-Phenyl	p-Cl-Phenyl	Methyl	OMe	OMe	CH	O	O	
72	OH	p-Me-O-Phenyl	p-Me-O-Phenyl	Methyl	OMe	OMe	CH	O	O	
73	OH	p-Me-O-Phenyl	p-Me-O-Phenyl	Ethyl	OMe	OMe	CH	O	O	
74	OH	p-Me-Phenyl	p-Me-Phenyl	Methyl	OMe	OMe	CH	O	O	
75	OH	p-Me-Phenyl	p-Me-Phenyl	Methyl	OMe	$O-CH_2-CH_2-C$		O	O	
76	OH	m-CF_3-Phenyl	m-CF_3-Phenyl	n-Propyl	OMe	OMe	CH	O	O	
77	OH	m-CF_3-Phenyl	m-CF_3-Phenyl	n-Propyl	OMe	$O-CH(CH_3)-CH_2-C$		O	O	
78	OH	p-NO_2-Phenyl	p-NO_2-Phenyl	Methyl	OMe	OMe	CH	O	O	
79	OH	p-NO_2-Phenyl	p-NO_2-Phenyl	Methyl	OMe	O-CH=CH-C		O	O	
80	OH	m-Cl-Phenyl	m-Cl-Phenyl	Ethyl	OMe	OMe	CH	O	O	
81	OH	o-F-Phenyl	o-F-Phenyl	Methyl	OMe	OMe	CH	O	O	

No.	R^1	R^4	R^5	R^6	R^2	R^3	X	Y	Z	m.p.[°C]
82	OH	o-F-Phenyl	o-F-Phenyl	Methyl	OMe	OMe	CH	S	O	
83	OH	o-Me-O-Phenyl	o-Me-O-Phenyl	Methyl	OMe	OMe	CH	O	O	
84	OH	o-Me-O-Phenyl	o-Me-O-Phenyl	Methyl	OMe	OMe	CH	O	S	
85	OH	3,4-Dimethoxyphenyl	3,4-Dimethoxyphenyl	Methyl	OMe	OMe	CH	O	O	
86	OH	3,4-Dioxomethylenephenyl [sic]	3,4-Dioxomethylenephenyl [sic]	Methyl	OMe	OMe	CH	O	O	
87	OH	p-CF_3-Phenyl	p-CF_3-Phenyl	Methyl	OMe	OMe	CH	O	O	
88	OH	Phenyl	Phenyl	Methyl	OMe	OEt		O	O	
89	OMe	Phenyl	Phenyl	Methyl	OMe	OEt		S	O	
90	OH	Phenyl	Phenyl	Ethyl	OMe	NH-OMe		O	O	
91	OH	p-Me-O-Phenyl	p-Me-O-Phenyl	n-Propyl	OMe	OCF_3		O	O	
92	OH	Phenyl	Phenyl	Methyl	OMe	CF_3		O	O	
93	OH	Phenyl	Phenyl	Methyl	OMe	CF_3		O	O	
94	OH	3,4-Dimethoxyphenyl	3,4-Dimethoxyphenyl	Benzyl	Me	Me		O	O	

No.	R^1	R^4	R^5	R^6	R^2	R^3	X	Y	Z	m.p.[°C]
95	OH	3,4-Dimethoxyphenyl	3,4-Dimethoxyphenyl	Methyl	OMe	O-CH_2-CH_2-C		O	O	
96	OH	Phenyl	Phenyl	Methyl	OMe	O-CH_2-CH_2-C		O	O	126 (decomp.)
97	OH	Phenyl	Phenyl	Methyl	OMe	O-CH(CH_3)-CH_2-C		O	O	
98	OH	Phenyl	Phenyl	Methyl	OMe	N(CH_3-CH=CH-C		O	O	118
99	OH	Phenyl	Phenyl	Methyl	OMe	S-C(CH_3)=C(CH_3)-C		O	O	
100	OH	Phenyl	Phenyl	Methyl	OMe	O-C(CH_3)=CH-C		O	O	
101	OH	Phenyl	Phenyl	Methyl	Me	O-C(CH_3)=CH-C		O	O	
102	OH	Phenyl	Phenyl	Methyl	Me	O-CH=CH-C		O	O	
103	OH	Phenyl	Phenyl	Methyl	Me	S-CH=CH-C		O	O	
104	OH	Phenyl	Phenyl	H	OMe	OMe	CH	O	O	
105	OH	Phenyl	Phenyl	Methyl	OMe	CH_2-CH_2-CH_2-C		O	O	
106	OH	Phenyl	Phenyl	Methyl	Methyl	CH_2-CH_2-CH_2-C		O	O	
107	OH	Phenyl	Phenyl	Methyl	Ethyl	CH_2-CH_2-CH_2-CH_2-C		O	O	



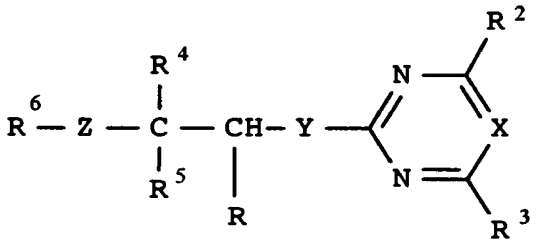
No.	R^1	A	R^6	R^2	R^3	X	Y	Z	m.p.[°C]
108	OH	Bond	Methyl	OMe	OMe	CH	O	O	
109	OH	CH_2	Methyl	OMe	OMe	CH	O	O	
110	OH	CH_2-CH_2	Methyl	OMe	OMe	CH	O	O	
111	OH	CH=CH	Methyl	OMe	OMe	CH	O	O	
112	OH	O	Methyl	OMe	OMe	CH	O	O	
113	OH	S	Methyl	OMe	OMe	CH	O	O	
114	OH	NH(CH_3)	Methyl	OMe	OMe	CH	O	O	
115	OH	Bond	Isopropyl	OMe	OMe	CH	O	O	
116	OH	Bond	p-Isopropylphenyl	OMe	OMe	CH	O	O	
117	OH	Bond	Benzyl	OMe	OMe	CH	O	O	
118	OH	CH=CH	Ethyl	OMe	OMe	CH	O	O	
119	OH	CH=CH	$(CH_3)_2$-CH_2-CH_2	OMe	OMe	CH	O	O	
120	OH	CH=CH	Cyclopropyl methylene	OMe	OMe	CH	O	O	
121	OH	CH=CH	Methyl	OMe	O-CH_2-CH_2-C		O	O	

No.	R^1	A	R^6	R^2	R^3	X	Y	Z	m.p.[°C]
122	OH	CH_2-CH_2	Ethyl	OMe	O-CH=CH-C		O	O	
123	OH	$CH_2=CH_2$	Methyl	OMe	$CH_2-CH_2-CH_2-C$		O	O	

Novel carboxylic acid derivatives, their preparation and use

Abstract

Carboxylic acid derivatives



where R-R^6, X, Y and Z have the meanings stated in the description, and the preparation thereof, are described. The novel compounds are suitable for controlling diseases.